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Testimony before the Health Subcommittee
Committee on Energy and Commerce
U.S. House of Representatives
on Programs Affecting Safety and Innovation in Pediatric Therapies
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Thank you for the opportunity to address the Subcommittee on the critical issue of the safety of pediatric therapies. My comments today will address XXX principal areas: a. how to ensure that studies of pediatric drugs and biologics are indeed conducted; and b. issues surrounding the approval of medical devices, including for children.

Much of the testimony you will have heard this morning will have extolled the successes of the current system for ensuring pediatric studies of drugs and biologics. To simplify somewhat, the system consists of a carrot and a stick. The carrot is the Best Pharmaceuticals for Children Act (BPCA) of 2002,[1] which grants six additional months of marketing exclusivity to companies that conduct pediatric studies consistent with a Written Request issued by the Food and Drug Administration (FDA). The stick is in effect a codification of an FDA regulation known as the Pediatric Rule, which was successfully challenged in the courts; that ruling was later appealed. In the interim, Congress passed the largely similar Pediatric Research Equity Act (PREA) which contains the essential elements of the Pediatric Rule: the ability of the FDA to require pediatric studies whenever a sponsor seeks approval for a new ingredient, indication, dosage form, dosing regimen or route of administration.

The successes of the present system are clear enough: 299 Written Requests, many of which would never have taken place without the Acts, 110 patent extensions and 90 labeling changes as of May 2005. (The number of relabelings has now risen to 128.) Yet, the question is not whether the system has had successes. Rather, it is whether a. it could have been more successful and b. whether these successes (or more) could have been obtained through alternate methods. Let us take these issues in turn.

While many studies have been undertaken, significant gaps remain. The biggest deficiency has occurred with respect to drugs that are off patent. This should surprise no-one. Tellingly, the data on off-patent drugs in the Government Accountability Office's (GAO's) report on the BPCA has been relegated to an appendix. (PREA has little impact upon off-patent drugs.) But the results are disconcerting. Following the process outlined under the BPCA, the National Institutes of Health (NIH) had by 2005 identified 40 off-patent drugs for which pediatric studies would have been useful. Yet the FDA issued

[1] BPCA was actually a successor to the exclusivity provisions in the Food and Drug Modernization Act of 1997.

Written Requests for only 16 of these and the drug sponsors declined to conduct all but one of them. While the NIH had funded seven of the remaining 15, that still leaves the great majority (83%) of the NIH's list unstudied. In part, this is because the NIH has received no appropriations for these pediatric studies.

Even with respect to on-patent drugs, significant deficiencies remain. According to the GAO, between 2002 and 2005 sponsors declined 41 of 214 (19%) Written Requests from the FDA, presumably because they did not think it was in their financial interest to conduct them. This is an underestimate of the extent to which companies are not complying with the FDA's priorities in that many of the Written Requests are in fact generated at the suggestion of the sponsor; presumably these are not being declined. BPCA does provide a mechanism for the study of drugs for which Written Requests have been declined: FDA can refer such studies to the Foundation for the National Institutes of Health (FNIH). This mechanism has been an abject failure. Of the 41 declined Written Requests, FDA referred only nine to the FNIH, which in turn had funded none of them.

The third area of deficiency relates to the kinds of diseases being studied. Since the majority of sales for most drugs will be derived from adult sales, fundamental economic principles would predict that companies would undertake pediatric studies (and thus expect exclusivity under the BPCA) in relation not to their pediatric sales, but to their adult sales. Using two different data sources, the GAO determined that only four or five of the ten most commonly prescribed pediatric drugs were studied under the BPCA. Possibly, the FDA did not issue Written Requests for all the remaining drugs (this seems to us unlikely) and quite likely these drugs are off-patent, but we will never know because FDA holds the Written Requests and the names of drugs being studied as confidential.

A group of researchers in the Netherlands, where a law similar to the BPCA has been enacted, studied the U.S. experience. They found that the diseases for which drugs were most frequently granted pediatric exclusivity were for the treatment of depression and mood disorders, hypertension, elevated cholesterol, HIV and pain. In general, they concluded, "The distribution of the different drugs closely matched the distribution of these drugs over the adult market, and not the drug utilization by children." (Boots, et al. European Journal of Pediatrics, January 17, 2007) [Sid: I have only the abstract for this and am trying to get the full article. OK to cite? I think so.]

With significant deficiencies in the study of both off-patent and on-patent drugs, and a profile of studies that leaves many important pediatric conditions neglected, it is clear that, whatever its successes, the current system is far from perfect.

The second major question I identified is whether the successes can be realized through other means. Specifically, are the current patent extensions too generous or, more fundamentally, are they needed at all? Here we turn to the PREA, the exemplar of the stick approach to this issue.

Although only enacted in December 2003, the PREA has already produced 55 changes in drug labels. Like the labeling changes under the BPCA, these changes have ranged from new indications to proof of lack of efficacy in certain subgroups to better description of the drug's adverse event profile in the pediatric population. All of this was obtained without the patent extensions that are at the core of the BPCA.

Recently published research[2] indicates that the exclusivity provisions under the BPCA are absurdly generous, at least for some drugs. The authors studied nine drugs from a variety of disease categories. For the current six-month patent extension, the economic returns (after subtracting out the costs of the trials) were as high as $508 million, with a median of $134 million; only one drug did not produce a financial gain from conducting the studies (loss of $8.9 million on $28.3 million in annual sales). One drug product, with $3.8 billion in annual sales, produced economic benefits to the sponsor 74 times as high as its expenses (median for all drugs: 12.4 times). Even with the patent extension reduced to three months, only one company had expenditures that exceeded the value of the exclusivity (median for all drugs: 5.7-fold). The version of PDUFA recently passed I the Senate reduces the term of the patent extension to three months for drugs with sales exceeding $1 billion in any year prior to the time the sponsor agrees to the Written Request. This is a move in the right direction, but still seems generous.

[Add: dollars involved. Who will pay.]

Unless there is a strong reason to believe that pediatric usage will be minimal, conducting pediatric studies should be seen as the responsibility of all companies seeking to market a drug, not an undertaking for which companies should be rewarded, let alone as generously as they currently are. Moreover, the FDA should have the authority to compel such studies, no matter what the stage in the drug's lifespan, without having to resort to patent extensions. This authority would extent to old and new drugs, to on-patient and off-patent drugs. The sole exception would be for drugs in which the pediatric use is off-label. In this case, a patent extension would be justified, but should not exceed three months for any drugs and should be still lower for those with annual sales in excess of $1 billion.

[To be added: transparency, publication bias and registry, delays in changing the label]

The issues with respect to pediatric medical devices are generally similar to those raised by pediatric drugs (lack of studies, devices too large, improper extrapolation from adult studies, etc.), but the issues we would like to raise apply equally to adult and pediatric devices.

The first problem is that the approval standard for devices that treat diseases is lower than that for drugs. Thus, to receive permission to be marketed, a drug must demonstrate "substantial evidence of effectiveness for the claimed indications,"[3] whereas a device

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[2] Li JS, Eisenstein EL, Grabowski HG, et al. Economic return of clinical trials performed under the pediatric exclusivity program. Journal of the American Medical Association 2007;297:480-8.

[3] 21 CFR 314.50(d)(5)(v)

need only demonstrate a "reasonable assurance that the device is safe and effective."[4] Thus data that could never support the approval of a drug can result in the approval of a device used to treat the same condition, potentially diverting patients from effective drugs to the device. A concrete example of this was the vagus nerve stimulator, approved by the Center for Devices and Radiological Health (CDRH) for treatment-resistant depression. According to a report from the Senate Finance Committee,[5] officials in the Center for Drug Evaluation and Research advised CDRH that if it had received similar data for an antidepressant drug, it would not have sanctioned even the filing of a New Drug Application.

[Add: 510(k) for Class III devices now the rule not the exception. Also, did you know that you can go 510(k) without even using the same mechanism of action?

A device is substantially equivalent if, in comparison to a predicate it:

- has the same intended use as the predicate; **and**
- has the same technological characteristics as the predicate;
  or
- has the same intended use as the predicate; **and**
- has different technological characteristics and the information submitted to FDA;
  - does not raise new questions of safety and effectiveness; **and**
  - demonstrates that the device is at least as safe and effective as the legally marketed device.

I plan to get into this and use rTMS as an example]

[4] 21 CFR 860.7(4)(c)(1)

[5] Committee on Finance, United States Senate. Review of the FDA's approval process for the vagus nerve stimulation therapy system for treatment-resistant depression. February 2006. Available at: http://finance.senate.gov/press/Gpress/02_2006%20report.pdf.